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ISSUE HIGHLIGHTS

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Happy Easter, Happy Spring!

Hepatitis A Vaccine Approval

The Food and Drug Administration (FDA) recently approved an inactivated hepatitis A vaccine (Havrix® - SmithKline Beecham) to be marketed in the U.S. This approval comes at an opportune time given the current shortage of intramuscular (IM) immunoglobulin. Immunoglobulin has been the standard prophylaxis for hepatitis A.[1] Historically, repeated epidemics of hepatitis A infection have occurred during wartime, thus the need to protect military personnel from disease is well recognized. Because of this threat of hepatitis A infection during times of deployment, the military has played an active role in the development and testing of hepatitis A vaccine.[2]

The Hepatitis A virus (HAV) is highly contagious and is transmitted person-to-person by the fecal-oral route. The virus has been shown to be spread: (1) through contaminated food or water (particularly raw or undercooked shellfish from contaminated waters); (2) after a breakdown in usual sanitary conditions; (3) during travel to areas of the world with poor hygienic conditions; (4) among institutionalized persons; and (5) in day-care centers.[3]

The vaccine is indicated for active immunization against HAV infection in persons $\geq$ 2 years of age. Persons who are at increased risk of infection include[3]:

- Persons traveling or relocating to areas of higher endemicity for hepatitis A, including military personnel
- Ethnic and geographic populations that experience cyclic hepatitis A epidemics, such as Alaskan Natives and American Indians
- Persons engaging in high-risk sexual activity
- Users of illicit injectable drugs
- Employees of child day-care centers
- Laboratory workers who handle primate animals that may harbor HAV or who handle live HAV

Primary immunization in adults consists of a single 1 mL IM dose of 1440 EL.U. (ELISA units). Children aged 2 to 18 years should

receive two 0.5 mL IM doses of 360 EL.U. each, given 1 month apart. All patients should receive a booster dose 6 to 12 months after primary immunization. Primary immunization should be completed at least 2 weeks prior to expected exposure to HAV.

Clinical trials have shown that protection against hepatitis A occurs within several weeks after the first dose of the vaccine in adults. Additionally, 99% of children seroconverted following two doses of the vaccine.[3] The protection provided by the vaccine is reported to last at least 4 years and is estimated to last as long as 15 years,[1] but follow-up studies are needed to further determine the duration of protection provided by the vaccine.

Hepatitis A vaccine may be administered concomitantly with immunoglobulin in persons requiring both immediate and long-term protection; however, the antibody titer is likely to be lower than when the vaccine is given alone. Immunoglobulin should be administered with a different syringe at a different injection site.[3]

Availability and pricing information is listed below.

NDC No.	*Description*	*FSS Price*
58160-835-02	Havrix® 1440 EL.U./1 mL prefilled syringe, 1s	$32.59
58160-836-01	Havrix® 360 EL.U./0.5 mL single-dose vial, 1s	available at the end of April 1995*
58160-835-01	Havrix® 1440 EL.U./1 mL single-dose vial, 1s	no information on availability at this time*

* personal communication, SmithKline Beecham Customer Satisfaction, March 27, 1995

Recommendations for the use of the vaccine are being prepared by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics. The PEC will publish these recommendations as they become available. Additionally, the Armed Forces Epidemiological Board has determined the vaccine to be a useful addition to current immunization guidelines for military personnel. The individual services are in the process of determining HAV immunization requirements for each service.

References:
1. F-D-C Reports 1995;57(11):5-6.
2. Hoke CH, et al. Vaccine 1992;10(Suppl 1):S75-S79.
3. Hepatitis A Vaccine, Inactivated Package Insert. SmithKline Beecham, 1995.

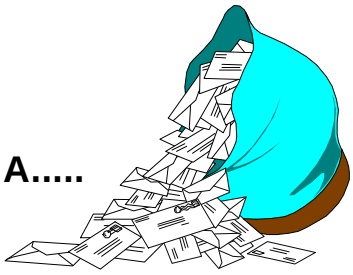
PEC Newsletter Survey

Thank you to everyone who responded to the PEC newsletter survey enclosed with PEC Update 95-01 in October 1994. We have reviewed your responses and comments and are working to make sure the Update contains information you can use.

If you have comments concerning the content of the PEC Update, or have suggestions for future Update articles, please do not hesitate to contact the PEC.

From the Mailbag:

PEC Q & A.....



Q: In the treatment of otitis media, the PEC recommends that second tier antibiotics should only be used in the event of treatment failure or allergies to all relevant first tier agents. My usual approach is to try the first tier antibiotic once. If this fails, I prescribe a second tier antibiotic. By trying to save the cost of second tier antibiotics, we may end up seeing the patient more frequently in the clinic.

A: The heart of this question lies in a larger question: When a child is symptomatic again with otitis media, is this a new, unrelated infection or a recrudescence of the original organism? If it is a new infection and antibiotic therapy is warranted, a first tier agent (e.g., amoxicillin) should be

effective. A recrudescence of the same organism would suggest either viral origin or an organism not responsive to the first agent used. In this case, if amoxicillin were the first agent used, an agent such as a sulfa or sulfa/macrolide combination would be a good choice as these drugs have an extended spectrum when compared to amoxicillin. Research is lacking to answer the larger question of new infection versus recurrence of the original infection.

The 'Pollyanna phenomenon'[1] is also applicable in this situation. Acute otitis media resolves without antibiotic therapy in a significant percentage of patients and persists even if treated with appropriate antibiotics in an equally significant percentage of patients. The end result is a convergence of clinical effectiveness for antibiotics with widely dispersed bacteriological efficacies. Drugs with high bacteriological efficacies tend to have lower clinical effectiveness due to other factors, such as viral illness. Conversely, drugs with low bacteriological efficacies have higher clinical effectiveness because of the self-limiting nature of the disease. This explains why newer antibiotics are often promoted with data showing in vitro efficacy against bacterial organisms.

Additionally, a trial from The Netherlands[2] demonstrated that symptomatic treatment (self-care) is effective for most children with acute otitis media (over 90% of 4860 children) and that their symptoms resolved within 3 to 4 days. Children with symptoms lasting more than 3-4 days were treated with either antibiotics or myringotomy. A recent meta-analysis[3] showed a modest impact from antibiotics on the clinical resolution of acute otitis media. β-lactamase resistant antibiotics did not increase resolution of acute symptoms or resolution of middle ear effusion. These type of data support the use of an "advice" line and self-care materials for initial symptomatic treatment by parents for children with these community-acquired, self-limiting illnesses.

1. Marchant CD, Carlin SA, Johnson CE, Shurin PA. Measuring the comparative efficacy of antibacterial agents for acute otitis media: the "Pollyanna phenomenon." *J Pediatr* 1992;120:72-7.

2. van Buchem FL, Peeters MF, van't Hof MA. Acute otitis media: a new treatment strategy. *BMJ* 1985;290:1033-7.

3. Rosenfeld RM, Vetrees JE, Carr J, et al. Clinical efficacy of antimicrobial drugs for acute otitis media: meta-analysis of 5400 children from 33 randomized trials. *J Pediatr* 1994;124:355-67.

Q: I received notification from the manufacturer that terazosin tablets (Hytrin® - Abbott) are being reformulated into a capsule dosage form. How does this affect the Tri-Service Formulary (TSF) status of terazosin since the tablet formulation was added to the TSF?

A: Many factors are evaluated when the PEC recommends a drug for the TSF. When the clinical and economic characteristics are essentially 'equal' among comparative drugs, other factors must be considered. These factors include, but are not limited to, current utilization of a drug at medical treatment facilities, use in unique military patient groups (e.g., aviators), drug-drug interactions, pharmacokinetic parameters, or other FDA indications of the drug.

Terazosin was added to the TSF based on an evaluation of these additional factors. At the time of the hypertension evaluation, terazosin was also the only alpha-1 adrenergic inhibitor with an indication for the treatment of benign prostatic hyperplasia (doxazosin recently received approval for this indication as well).

The change in the dosage formulation of terazosin does not appear to alter patient compliance with the drug. Additionally, the new capsules are available in the same dosage strengths and at the same price as the original tablets. Because a 'half-tablet' dosing strategy was not used in the hypertension analysis, the dosage form is of no consequence (see PEC Update 95-04 for more detail on 'half-tablet' dosing). For these reasons, there is no need to re-do the hypertension analysis at this point. Thus, in this case, terazosin remains the TSF alpha-1 adrenergic blocker of choice and the tablet dosage form is simply converted to the capsule formulation.

Product and Price Comparison Tool Update

Purchasers of pharmaceuticals in the Military Health Services System now have the option to buy products from prime vendors, the Defense Personnel Support Center (Depot or SPEDE), or direct from manufacturers using the Federal Supply Schedule (FSS) for items not covered by the prime vendor contract. In addition to price, another important component of drug product purchasing is the therapeutic equivalence rating of generic drugs as determined by the Food and Drug Administration (FDA) (see PEC Update 94-06).

The Product and Price Comparison (PPC) Tool is a computer software program developed by the Defense Medical Logistics Standard Support (DMLSS) Program which offers a quick and easy way to determine both the lowest price and the therapeutic equivalence rating for a specific product. The software requires a stand-alone personal computer (PC) running MS-DOS with at least 30 MB of free hard disk space and is updated monthly.

Once the PPC is installed on a PC, users can search for items by National Stock Number (NSN), nomenclature (generic or trade name), National Drug Code (NDC) number, or manufacturer. For example, you may want to find the source of supply with the lowest price and a therapeutic equivalence rating of "A" for propranolol 40 mg tablets. The search could be started by moving the cursor to the nomenclature field and entering any of the following: "prop", "propra", "propranolol", "Inde", or "Inderal".

The search engine employs truncation so it is not necessary to type the entire nomenclature. Alternatively, one could enter a specific NSN or NDC number. After entering the search criteria, you are given a list of all available propranolol dosage forms. Highlighting propranolol 40 mg tablets and hitting enter or return takes you to another screen displaying the various package sizes, prices, therapeutic equivalence ratings, manufacturers, and sources of supply. At this point, pharmaceutical purchasers should select the lowest priced product available from the prime vendor with an "A" therapeutic equivalence code.

The therapeutic equivalency codes in the PPC tool match those of the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the 'Orange Book', with the exception of "Z" codes. A code of "ZA" indicates a pharmaceutical entity that has been evaluated by the FDA, but the particular labeled product has not been evaluated (e.g., Rugby brand propranolol 40 mg). "ZB" codes are assigned to all nonprescription pharmaceuticals and legend pharmaceutical entities that have not been evaluated in the Orange Book (e.g., aspirin 325 mg tablets). "ZC" codes are usually assigned to single source drugs that do not have a therapeutic equivalency rating in the Orange Book (e.g., divalproex sodium 250 mg tablets). No conclusions regarding the equivalency of products with a "Z" rating can be made. For more information on the PPC Tool, please call the DMLSS Help Desk at 1-800-559-5459.

Purchasers should remember that transaction costs are incurred when products are ordered by local purchase versus prime vendor. These costs may negate potential savings from slightly lower priced products ordered in this manner. Therefore, facilities should not use the local purchase option for items available from the prime vendor.

Local Use of PEC Update Articles

Need ideas for your MTF pharmacy newsletter? Why not reprint articles published in the PEC Update. The PEC encourages local MTFs to disseminate the monthly Update information to all providers through local newsletters, P & T Committee meeting minutes, or other mechanisms.

Approval of Varicella Vaccine

The FDA recently approved a live attenuated vaccine against varicella-zoster virus (Varivax® - Merck), the virus that causes chicken pox. Varicella virus causes approximately 3.5 million cases of chicken pox annually, with the peak incidence in children 5 to 9 years of age. Additionally, over 9000 hospitalizations and up to 100 deaths per year are attributed to the infection.[1]

Clinical trials indicate that seroconversion or acquisition of detectable varicella antibodies occurred 4 to 6 weeks after vaccination in 97% of children (aged 12 months to 12 years). Breakthrough cases of chicken pox were observed in 0.2 to 1% of vaccinees per year. The incidence rate of chicken pox in unvaccinated children aged 1 to 9 years is estimated to be 8.3% to 9.1% per year.[1,2] Additionally, a 94% seroconversion rate has been reported in adolescents and adults 6 weeks after the first vaccination and a 99% seroconversion rate 6 weeks after a second vaccination.[1]

Short-term efficacy of the vaccine has been demonstrated in clinical trials, but the long-term effect of the vaccine has not been determined. Limited data suggest that immunity persists for at least 6 years following vaccination.[1] Additionally, the possibility of waning immunity raises concerns that adults who receive the vaccine in childhood will be at risk of developing zoster.[2] Herpes zoster cases have been reported during follow-up in clinical trials, and all cases were considered mild and without sequelae.[1] Other adverse effects include redness or swelling at the injection site, fatigue, or nausea.[3]

The manufacturer plans to conduct long-term post-marketing studies to evaluate the occurrence of rare adverse effects, breakthrough rates of chicken pox, herpes incidence, and whether booster vaccinations are needed.[1] Additionally, studies have begun evaluating combination varicella and measles-mumps-rubella vaccines.[2]

Although the package insert for the vaccine has not been finalized by the FDA at this time, the recommended dosage for children aged 12 months to 12 years is a single 0.5 mL injection. Adolescents and adults 13 years of age and older who have never had chicken pox should receive two 0.5 mL injections 4 to 8 weeks apart. Each 0.5 mL injection contains 1350 plaque forming units of virus.[1,3]

The Federal Supply Schedule price for the vaccine has not been established at this time. The average wholesale price for a single-dose 0.5 mL vial is $39.94. The vaccine is expected to be available during May 1995 (personal communication, Merck Federal Marketing, March 28, 1995).

A recent analysis[4] evaluated the economic consequences of a routine varicella vaccination program for healthy children. The analysis showed a routine vaccination program would result in net savings from a societal perspective when medical costs and work-loss costs of parents are considered.

Recommendations for the use of varicella vaccine are being prepared by the Advisory Committee on Immunization Practices. The PEC will publish these recommendations and additional pricing and dosing information as they become available.

References:
1. F-D-C Reports 1995;57(12):6-7.
2. Marwick C. JAMA 1995;273:833-6.
3. Managed Care Pharmacy FaxNews, 1995 Mar 21.
4. Lieu TA, et al. JAMA 1994;271:375-81.

Tri-Service Formulary Quick Reference Guide

An updated TSF Quick Reference Guide is provided on page 6 of this PEC Update. This version replaces the December 1994 version published in PEC Update 95-03. Two changes are reflected in this new version: (1) the removal of fluoxetine 20 mg capsules from the list because of its suspension from the TSF pending resolution of pricing issues related to the antidepressants, and (2) terazosin formulation change from tablets to capsules (see additional explanation on page 3 of this Update).

Tri-Service Formulary Quick Reference Guide

Antimicrobials / Antifungals
*amoxicillin oral suspension and caps
*Bactrim™/Septra® susp and tabs
*dicloxacillin oral
*doxycycline 100 mg caps
*erythromycin oral suspension and tabs or caps
*erythromycin/sulfisoxazole susp
*griseofulvin 125 mg tabs
*isoniazid 300 mg tabs
*metronidazole 250 mg tabs
*nystatin oral suspension
*penicillin VK susp and 250 mg tabs
*rifampin 300 mg caps
*tetracycline 250 mg caps

Antibiotics-EENT
*Cortisporin® Otic Suspension
*gentamicin ophth. soln. 0.3%
*Neosporin® Ophth. Solution
*sulfacetamide ophth. oint. 10%

Antivirals
acyclovir 200 mg caps

Anthelmintics
mebendazole 100 mg chew tabs

Antiulcer Drugs
*amoxicillin oral
*bismuth subsalicylate 262 mg tabs
*metronidazole 250 mg tabs
*tetracycline 250 mg caps

GERD Agents
cisapride 20 mg tabs
omeprazole 20 mg caps

Other GI Agents
*dicyclomine tabs or caps
*Donnatal® tabs
*sulfasalazine 500 mg tabs

Anti-diarrheals
*loperamide 2 mg tabs or caps

Genitourinary Agents
*oxybutynin 5 mg tabs
*phenazopyridine 100 mg tabs

Gout Agents
*allopurinol tabs
*probenecid 500 mg tabs

Muscle Relaxants
*diazepam 5 mg tabs
*methocarbamol 500 mg tabs

Nasal Corticosteroids
*beclomethasone nasal inhaler

Oral Corticosteroids
*prednisone 5 mg tabs
*prednisone 20 mg tabs

Asthma Agents
*albuterol oral inhaler
*beclomethasone oral inhaler
*terbutaline 5 mg tabs

Antihistamines / Decongestants
*Actifed® tabs
*chlorpheniramine 4 mg tabs
*chlorpheniramine syrup
*Dimetapp® Elixir
*Dimetapp® Extentabs
*diphenhydramine caps
*diphenhydramine syrup
*hydroxyzine syrup
*hydroxyzine tabs
*oxymetazoline nasal spray
*pseudoephedrine 30 mg tabs

Anticonvulsants
Dilantin® Infatabs 50 mg
Dilantin® Kapseals 100 mg
*phenobarbital elixir 20 mg/5 mL
*phenobarbital 30 mg tabs
*primidone 250 mg tabs
†Tegretol® 200 mg tabs

Anticoagulants
*warfarin 5 mg tabs

Diuretics
*furosemide 40 mg tabs
*hydrochlorothiazide tabs
*Maxzide® tabs
*spironolactone 25 mg tabs

Vasodilators
*isosorbide dinitrate 10 mg tabs
nitroglycerin sublingual tabs

Lipid Lowering Agents
*niacin tabs

Electrolyte Replacement
*potassium chloride slow release tabs or caps

Hypotensive / Cardiac Drugs
*atenolol tabs
*clonidine tabs
†Lanoxin® 0.25 mg tabs
lisinopril tabs
*propranolol 10 & 40 mg tabs
*quinidine gluconate 324 mg tabs
*quinidine sulfate tabs
terazosin caps
*verapamil long-acting tabs

Diabetic Agents
*human insulin, regular & NPH

NSAIDS / Analgesics
*acetaminophen drops, elixir, and 325 mg tabs
*aspirin, enteric-coated 325 mg tabs
*ibuprofen susp and 400 mg tabs
*indomethacin 25 mg caps
*Tylenol #3® tabs

Migraine Agents
*Cafergot® tabs
*Fiorinal® tabs
*Midrin® caps

Attention Deficit / Narcolepsy Agents
*methylphenidate 10 mg tabs
*methylphenidate sustained release 20 mg tabs

Contraceptives
LoOvral®
*Norinyl 1+50®, Ortho-Novum 1/50®
*Ortho-Novum 1/35®, Norinyl 1+35®
Ortho-Novum 7/7/7®
Ovral®
Triphasil®/Tri-Levlen®

Estrogens / Progestins
conjugated estrogens 0.625 mg tabs
conjugated estrogen vaginal cream
*medroxyprogesterone 10 mg tabs

Thyroid / Antithyroid Agents
*propylthiouracil 50 mg tabs
†Synthroid® 100 mcg (0.1 mg) tabs

Topical Agents
*bacitracin ointment
*hydrocortisone 1% cream
Sebutone® shampoo
*Selsun® shampoo

Vitamins & Minerals
*ferrous sulfate concentrated soln. 125 mg/mL
*ferrous sulfate 325 mg tabs
*pyridoxine 50 mg tabs

Miotics
*pilocarpine ophth. solution

Miscellaneous
insect sting kit

generic products are available
†***DMSB sole source item***

Brand names are included for example only and are not meant to imply the recommendation of a specific product except for those products designated as sole source items by the Defense Medical Standardization Board.

Updated March 1995